Vegetables, fruit, and antioxidant-related nutrients and risk of non-Hodgkin lymphoma: a National Cancer Institute–Surveillance, Epidemiology, and End Results population-based case-control study[1–3]

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ABSTRACT

Background: Factors related to DNA damage and altered immunologic responses, such as reactive oxygen species production, are associated with the risk of non-Hodgkin lymphoma (NHL).

Objective: The aim was to evaluate NHL risk with intakes of vegetables, fruit, and nutrients involved in antioxidant activities.

Design: Incident case subjects aged 20–74 y were identified between 1998 and 2000 from a National Cancer Institute–sponsored study by using four Surveillance, Epidemiology, and End Results registries. Control subjects, who were selected by random dialing (<65 y) and from Medicare files (≥65 y), were matched to cases by age, center, race, and sex. Of 1321 case and 1057 control subjects who enrolled, dietary data were collected on a subset (466 cases and 391 controls). Carotenoid intakes were estimated by using updated values from the US Department of Agriculture nutrient databases. Unconditional logistic regression models were used to estimate odds ratios (ORs) and 95% CIs.

Results: NHL risk was inversely associated with higher number of weekly servings of all vegetables (multivariable OR for highest compared with lowest quartile: 0.58; 95% CI: 0.35, 0.95; *P* for trend = 0.04), green leafy vegetables (OR: 0.59; 95% CI: 0.36, 0.96; *P* for trend = 0.01), and cruciferous vegetables (OR: 0.62; 95% CI: 0.39, 1.00; *P* for trend = 0.05) and with higher daily intakes of lutein and zeaxanthin (OR: 0.54; 95% CI: 0.32, 0.91; *P* for trend = 0.06) and zinc (OR: 0.58; 95% CI: 0.36, 0.91; *P* for trend = 0.02). An effect modification by exercise and NHL subtype was observed with some food groups and nutrients.

Conclusion: Higher intakes of vegetables, lutein and zeaxanthin, and zinc are associated with a lower NHL risk. *Am J Clin Nutr* 2006;83:1401–10.

KEY WORDS Anticarcinogenic agents, cruciferous vegetables, carotenoids, diet, neoplasms, zinc

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignancies that are characterized by proliferation of T or B cells; most of these cancers originate from B cells. The age-adjusted incidence of NHL increased from 11.1 per 100 000 persons in 1975 to 19.3 per 100 000 persons in 2002, and NHL had one of the fastest rising cancer rates during this time period (1). The reason for this increase is largely unknown. Studies have consistently shown strong associations with factors related to altered immunologic responses (2). Reactive oxygen species (ROS) production such as superoxide radicals, hydrogen peroxide, and hydroxyl radicals can alter DNA and lipid membrane structures, particularly in proliferating cells such as those involved in the immune system, which suggests a protective effect of nutrients involved in antioxidant activities against NHL.

Epidemiologic studies that investigated the association between NHL and vegetables, fruit, and the nutrients found in these foods reported inverse associations with increased intakes of all vegetables combined (3, 4), cooked tomato products (5), green leafy vegetables (4, 6), and cruciferous vegetables (3–5), although other studies reported no (7–9) or elevated (10, 11) risk. Some studies described inverse associations with higher fruit intake (4, 6, 7, 10), whereas others found null associations (3, 5, 8, 9, 12). Most studies have not supported an inverse association between NHL risk and dietary or supplemental intake of vitamins A, C, or E (3, 5, 7, 13) or individual carotenoids (3, 5, 7). Variations in dietary assessment, study design, sample size, or analyses may have contributed to the different findings. For example, not all studies controlled for total energy, and energy imbalance has been associated with NHL in some studies (14). Furthermore, micronutrients such as zinc have not been studied, and few investigated carotenoids other than α- and β-carotene (3), particularly in NHL subtypes. Therefore, we evaluated the associations

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between antioxidant and related nutrient intakes, as well as the food sources of these nutrients, and the risk of NHL using detailed dietary and risk factor data collected from a large, multicentered, population-based case-control study of NHL conducted in the United States.

SUBJECTS AND METHODS

Study design and population

Between 1998 and 2000, 1321 of 2248 (59% response) potentially eligible incident case subjects aged 20 to 74 y with NHL and without evidence of HIV infection were enrolled from National Cancer Institute–sponsored Surveillance, Epidemiology, and End Results registries in Iowa, Seattle, Los Angeles, and Detroit. Population control subjects aged <65 y without history of NHL were identified by random dialing and those aged ≥65 y were identified from Medicare files. Controls were frequency-matched to cases by age (5 y), center, race, and sex. Of 2409 potentially eligible controls, 1057 (44%) were enrolled. Details of the study are presented elsewhere (15). All respondents provided informed consent, and the study protocol was approved by each center's Institutional Review Board.

Risk factors and dietary assessment

The study population was divided into 2 groups; each group received a different version of a computer-assisted personal interview and a different self-administered questionnaire. A split study design was employed to maximize the amount of data collected. Both versions of the computer-assisted personal interview contained questions about demographic characteristics, hair coloring, occupational history, and pesticide use. One version (administered to all African Americans and 50% of non–African Americans) also included an extended medical history and use of illicit drugs; persons assigned to this group were mailed a self-administered questionnaire on family medical history. The other version of the computer-assisted personal interview (administered to the other 50% of non–African Americans) included questions about cell phone use, sun exposure, hobbies, and an abbreviated medical history; persons assigned to this group were mailed a self-administered questionnaire on dietary intake as assessed by a modified Block 1995 Revision of the Health Habits and History Questionnaire (16, 17). For each food, participants were asked to indicate their usual portion from a selection of 3 serving sizes and how often, on average, they had consumed that amount over the past year. The 9 responses ranged from "never or less than once per month" to "every day". In addition, the participants provided information about the regular use of multivitamins, defined as ≥ 1 pill/wk, over the past year. Regular multivitamin consumers were then queried about their frequency of use according to 4 categories, which ranged from never to every day, and about their duration of use according to 6 categories, which ranged from <1 y to ≥10 y. The same information was requested for 8 single vitamin and mineral preparations (including vitamin A, β-carotene, and zinc). Information about the type of multivitamin consumed [One-A-Day (Bayer corporation, Research Triangle Park, NC)- or Centrum (Wyeth, Madison, NJ)-type compared with antioxidant-type, and multivitamins with or without minerals] was obtained, and standard doses were applied to each type of multivitamin preparation. For vitamins C and E, information on the usual dose was collected. For individual supplements excluding vitamins C and E, the following values were assigned to each vitamin or mineral: 10 000 IU for vitamin A, 25 000 IU for β-carotene, and 50 mg for zinc. We used the updated 1998 US Department of Agriculture–National Cancer Institute Carotenoid Database (http://www.nal.usda.gov/fnic/foodcomp/Data/Carot/) to evaluate the α- and β-carotene, lycopene, β-cryptoxanthin, and lutein and zeaxanthin content of fruit, vegetables, and multicomponent foods that contained fruit and vegetables; these values were supplemented with the 1993 values (18–20) when 1998 values were unavailable. Daily intakes of nutrients were calculated by summing the product of the frequency of consumption of the serving of each food by the nutrient content of that serving of food across all food items. The present analysis is based on persons who returned the dietary questionnaire. This included 482 of 552 cases and 417 of 462 controls who were assigned to the dietary group plus 2 other cases and 2 other controls who inadvertently received and returned the dietary questionnaire, for a total of 484 cases and 419 controls. We excluded subjects if the daily number of reported foods on the questionnaire was <4 or >30 for the men and <3 or >30 for the women or if the number of food items missing or left blank exceeded 20% (21–24); in total, 18 cases and 28 controls were excluded.

Statistical analysis

Individual foods were grouped according to similar nutrient content or genus classification and expressed as weekly servings. Food groups and individual nutrients were modeled as categorical variables corresponding to the quartile distribution of intake in the control group. We calculated odds ratios (ORs) and 95% CIs with unconditional logistic regression using the lowest category of intake as the referent. For each dietary variable, we ran 2 statistical models. The first was adjusted for age (<35, 35–44, 45–54, 55–64, or ≥65 y), sex, race (White, Asian, or other), study center (Detroit, IA, Los Angeles, or Seattle), and quartiles of total energy intake. The second was adjusted for the aforementioned variables and for potential confounders and variables that were suspected of being associated with NHL: smoking (nonsmoker, <7, 7–16, 17–34, or ≥35 pack-years), family history of NHL, body mass index (in kg/m^2; <20, 20–24.9, 25–29.9, or ≥30), exercise [in weekly metabolic equivalents; no exercise, 30–270, 271–675, 676–1080, or >1080], education (<12, 12–15, or ≥16 y), quartiles of ethanol consumed (in g/wk), and quartiles of dietary fiber intake (in g/d), which was shown to be a potential confounder (5). A chi-square test for trend was conducted treating the categorical dietary variable as a continuous variable in the regression models (25). We also conducted polychotomous logistic regression (26) according to NHL subtype and simultaneously modeled the comparison between controls and each of the 2 most common NHL subtypes (follicular and diffuse) using the lowest category of dietary intake as the referent. Heterogeneity of the dietary NHL subtype associations was tested by case-only analysis of follicular compared with diffuse subtypes (27). Secondary analyses evaluated the extent of effect modification by level of the covariates with the likelihood ratio test between models that included and excluded a product term for the nutrient and effect modifier (28).

Before the logistic regression analysis, food groups and nutrients were adjusted for total energy by taking the residual from a linear regression model in which total energy intake was the independent variable and the dietary variable was the dependent

TABLE 1
Comparison of demographic characteristics between case and control subjects from the National Cancer Institute–Surveillance, Epidemiology, and End Results Study (1998–2000)

Characteristic	Control subjects (n = 391)	Case subjects (n = 466)	P^1
Age			< 0.0001
<35 y [n (%)]	12 (3)	26 (6)	
35–44 y [n (%)]	33 (8)	59 (13)	
45–54 y [n (%)]	61 (16)	99 (21)	
55–64 y [n (%)]	98 (25)	130 (28)	
≥65 y [n (%)]	187 (48)	152 (33)	
Sex			0.24
Men [n (%)]	195 (50)	251 (54)	
Race			0.45
White [n (%)]	375 (96)	441 (95)	
Asian [n (%)]	9 (2)	16 (3)	
Other [n (%)]	7 (2)	9 (2)	
Study center			0.52
Detroit [n (%)]	47 (12)	52 (11)	
Iowa [n (%)]	136 (35)	176 (38)	
Los Angeles [n (%)]	82 (21)	103 (22)	
Seattle [n (%)]	126 (32)	135 (29)	

[1] Comparison of case and control subjects with the Mantel-Haenszel chi-square test.

variable (29). Subsequent logistic regression models of NHL included total energy as a covariate. The ORs and 95% CIs from these models were compared with those from models that were adjusted for total energy by using the standard multivariable approach without the additional step of residual analysis. The 2 modeling approaches for energy adjustment generally estimated similar effect estimates with some exceptions (*see* Results). Given that models that use the standard multivariable method of energy adjustment may produce spurious associations in the presence of correlated errors (30), we present data on the energy-adjusted values from the residual method. Analyses were carried out with SAS version 8 (SAS Institute, Cary, NC) software systems. Two-sided P values < 0.05 were considered statistically significant.

RESULTS

Dietary data were analyzed for 466 cases and 391 controls. Comparable distributions for age, sex, race, and study center were observed between the cases and controls in the present analyses compared with all eligible cases (n = 2010) and all eligible controls (n = 2002; data not shown). A greater proportion of cases than controls were aged <65 y (**Table 1**). Differences in the intakes of total energy, total vegetables, specific vegetable categories, and for some nutrients were observed between cases and controls (**Table 2**).

The associations between food groups and NHL are presented in **Table 3**. Compared with those in the lowest quartile, persons in the highest quartile of vegetable intake (ie, ≥20 servings/wk) had a 42% lower risk of NHL after a multivariable analysis (P for trend = 0.04). Reduced risks were also observed with persons who consumed ≥6 servings green leafy vegetables/wk and for those who consumed ≥3 servings cruciferous vegetables/wk. Because higher vegetable consumption may simply be a marker of a healthy diet that is lower in meat and fat intakes, which have been reported to be associated with NHL in this (31) and other studies (3, 7), we additionally adjusted for servings of red, processed, and fried meats (beef, pork, processed meats, fried chicken, and fried fish); the ORs, however, were relatively unchanged (data not shown). Inverse associations were also observed with higher intakes of yellow, orange, and red vegetables and processed tomato products, but these associations were attenuated after adjustment for other variables. Intake of fruit and consumption of whole grains, a source of antioxidant-related nutrients, were not significantly associated with NHL (data not shown).

Of the nutrients, NHL risk was lowered by 46% with higher intakes of lutein and zeaxanthin after covariate adjustment (P for trend = 0.06), whereas NHL risk was not significantly related to intakes of vitamins A, C, and E and other dietary carotenoids (**Table 4**). After multivariable adjustment, inverse associations were observed between NHL risk and the highest quartile of zinc intake from dietary sources (P for trend = 0.02) and dietary plus supplemental zinc intake (P for trend = 0.08). The ORs for nutrients were not significantly changed after additional adjustment for intakes of saturated fat and polyunsaturated fat, nutrients that have previously been shown to be associated with NHL (5, 9).

To further examine whether the relations between vegetable, lutein and zeaxanthin, and zinc consumption and NHL risk were independent of other potential risk factors for NHL, we conducted multivariable analyses within strata that were defined by levels of these factors (**Table 5**). The lowest risk of NHL was consistently found in the most active and the leanest body mass index (<25) subgroup, although the P for interaction across all dietary variables by body mass index categories was not statistically significant (data not shown). Lower risks were also observed for the highest compared with the lowest quartiles of zinc intake in the women (OR: 0.34; 95% CI: 0.18, 0.64), but not in the men (OR: 0.92; 95% CI: 0.43, 1.96; P for interaction = 0.04).

We also examined the associations between food groups and nutrients and NHL risk by follicular and diffuse tumor subtype

TABLE 2
Risk factor and dietary characteristics between case and control subjects from the National Cancer Institute–Surveillance, Epidemiology, and End Results Study (1998–2000)[1]

Characteristic	Control subjects (n = 391)	Case subjects (n = 466)	P[2]
Family history of NHL in first-degree relatives			0.59
Yes [n (%)]	17 (4)	24 (5)	
Tobacco smoking (pack-years)[3]			0.70
Nonsmoker [n (%)]	171 (45)	214 (48)	
<7 pack-years [n (%)]	32 (8)	39 (9)	
7–16 pack-years [n (%)]	37 (10)	46 (10)	
17–34 pack-years [n (%)]	66 (17)	48 (11)	
≥35 pack-years [n (%)]	72 (19)	102 (23)	
Educational level			0.62
<12 y [n (%)]	36 (9)	34 (7)	
12–15 y [n (%)]	218 (56)	287 (62)	
≥16 y [n (%)]	137 (35)	145 (31)	
Physical activity index levels[4]			0.08
No exercise [n (%)]	55 (15)	84 (19)	
30–270 METS/wk [n (%)]	87 (23)	108 (24)	
271–675 METS/wk [n (%)]	81 (21)	94 (21)	
676–1080 METS/wk [n (%)]	81 (21)	70 (16)	
>1080 METS/wk [n (%)]	75 (20)	86 (19)	
BMI, kg/m^2 [median (IQR)][5]	26.2 (5.4)	26.0 (5.6)	0.66
Dietary intake			
Total energy, kcal/d [median (IQR)]	1646 (813)	1815 (908)	0.01
Alcohol, g/wk [median (IQR)]	8.6 (52.2)	0 (36.2)	0.003
Total fiber, g/d [median (IQR)]	12.8 (7.7)	13.3 (7.5)	0.88
All fruit including juices, servings/wk [median (IQR)][6]	14.9 (61.6)	14.7 (55.2)	0.19
All fruit excluding juices, servings/wk [median (IQR)]	11.7 (53.4)	11.1 (51.1)	0.07
Citrus fruit including juices, servings/wk [median (IQR)][7]	3.6 (50.9)	3.2 (49.9)	0.09
Citrus fruit excluding juices, servings/wk [median (IQR)]	0.6 (25.8)	0.6 (24.8)	0.15
Yellow, orange, and red fruit, servings/wk [median (IQR)][8]	4.2 (9.2)	3.7 (8.7)	0.29
All vegetables, servings/wk [median (IQR)][9]	14.7 (9.9)	12.4 (8.5)	< 0.0001
Yellow, orange, and red vegetables, servings/wk [median (IQR)][10]	1.5 (26.1)	1.3 (27.5)	0.003
Processed tomato products, servings/wk [median (IQR)][11]	2.7 (15.7)	2.5 (17.4)	0.05
Mixed foods with tomato products, servings/wk [median (IQR)][12]	1.6 (5.8)	1.6 (7.7)	0.75
Green leafy vegetables, servings/wk [median (IQR)][13]	3.8 (18.5)	2.3 (13.4)	< 0.0001
Cruciferous vegetables, servings/wk [median (IQR)][14]	1.6 (10.3)	1.2 (7.4)	0.0004
Dietary vitamin A, RE/d [median (IQR)]	990 (613)	1003 (675)	0.03
Dietary α-carotene, μg/d [median (IQR)]	250 (282)	228 (285)	0.01
Dietary β-carotene, μg/d [median (IQR)]	2394 (2137)	2274 (2063)	0.10
Dietary β-cryptoxanthin, μg/d [median (IQR)]	122 (184)	133 (179)	0.28
Dietary lutein and zeaxanthin, μg/d [median (IQR)]	1962 (1845)	1667 (1621)	0.0001
Dietary lycopene, μg/d [median (IQR)]	4283 (3378)	4537 (4237)	0.87
Dietary vitamin E, α-TE/d [median (IQR)]	8.3 (5.9)	8.9 (5.4)	0.23
Dietary vitamin C, mg/d [median (IQR)]	90.3 (68.6)	89.5 (67.1)	0.02
Dietary zinc, mg/d [median (IQR)]	9.8 (5.0)	10.3 (5.8)	0.005

[1] NHL, non-Hodgkin lymphoma; METS, metabolic equivalents; IQR, interquartile range; RE, retinol equivalents; α-TE, α-tocopherol equivalents.
[2] Comparison of case and control subjects with the Mantel-Haenszel chi-square test for categorical variables and the Wilcoxon nonparametric test for continuous variables.
[3] Data were missing from 17 case and 13 control subjects.
[4] Data were missing from 24 case and 12 control subjects.
[5] Data were missing from 17 case and 20 control subjects.
[6] Includes apples and applesauce, apple juice, bananas, grapefruit, cantaloupe, orange juice, orange juice with calcium, oranges, canned peaches, fresh peaches, prunes and prune juice, strawberries and other berries, watermelon, and other fruit.
[7] Includes grapefruit, orange juice, orange juice with calcium, and oranges.
[8] Includes cantaloupe, canned peaches, fresh peaches, watermelon, strawberries, and other berries.
[9] Includes alfalfa sprouts, beets, broccoli, carrots, cauliflower, Brussels sprouts, celery, corn, green beans, mustard greens, green salad, peas, radish, rhubarb, coleslaw, spinach, sweet potatoes, tomatoes and tomato juice, and other vegetables.
[10] Includes beets, carrots, rhubarb, and sweet potatoes.
[11] Includes tomatoes, tomato juice, and salsa.
[12] Includes chili, pizza, and spaghetti with tomato sauce.
[13] Includes mustard greens, green salad, and spinach.
[14] Includes broccoli, cauliflower, Brussels sprouts, coleslaw, mustard greens, and radishes.

TABLE 3
Odds ratios (ORs) and 95% CIs of the association between weekly servings of fruits and vegetables and non-Hodgkin lymphoma in the National Cancer Institute–Surveillance, Epidemiology, and End Results Study (1998–2000)

Food group	Control subjects	Case subjects	OR (95% CI)[1]	Multivariate model OR (95% CI)[2]
	n	*n*		
All vegetables (servings/wk)				
≤8	98	161	1.00	1.00
8.5–13	98	124	0.77 (0.52, 1.12)	0.84 (0.55, 1.29)
13.5–20	98	103	0.65 (0.44, 0.96)	0.78 (0.50, 1.22)
>20	97	78	0.51 (0.34, 0.78)	0.58 (0.35, 0.95)
P for trend			0.001	0.04
Yellow, orange, and red vegetables (servings/wk)				
≤0.5	98	159	1.00	1.00
1–1.5	98	113	0.73 (0.50, 1.07)	0.83 (0.54, 1.28)
2–3	98	110	0.78 (0.53, 1.15)	0.88 (0.58, 1.35)
>3	97	84	0.61 (0.41, 0.92)	0.68 (0.42, 1.11)
P for trend			0.03	0.18
Processed tomato products (servings/wk)				
≤1	98	153	1.00	1.00
1.5–2.5	98	105	0.68 (0.46, 1.00)	0.74 (0.48, 1.12)
3–4.5	98	109	0.63 (0.42, 0.92)	0.73 (0.47, 1.13)
>4.5	97	99	0.72 (0.49, 1.06)	0.79 (0.51, 1.22)
P for trend			0.07	0.29
Mixed foods with tomato products (servings/wk)				
≤0.5	98	121	1.00	1.00
1–1.5	98	108	0.86 (0.58, 1.27)	0.92 (0.59, 1.42)
2–2.5	98	125	0.92 (0.62, 1.37)	0.97 (0.63, 1.51)
>2.5	97	112	0.81 (0.54, 1.22)	1.02 (0.64, 1.60)
P for trend			0.40	0.90
Green leafy vegetables (servings/wk)				
≤1.5	98	168	1.00	1.00
2–3.5	98	127	0.78 (0.54, 1.14)	0.89 (0.58, 1.37)
4–6	98	90	0.49 (0.33, 0.74)	0.58 (0.36, 0.91)
>6	97	81	0.49 (0.32, 0.75)	0.59 (0.36, 0.96)
P for trend			0.0001	0.01
Cruciferous vegetables (servings/wk)				
≤0.5	98	147	1.00	1.00
1–1.5	98	126	0.88 (0.60, 1.28)	0.97 (0.64, 1.47)
2–3	98	115	0.86 (0.59, 1.27)	0.85 (0.55, 1.30)
>3	97	78	0.58 (0.38, 0.88)	0.62 (0.39, 1.00)
P for trend			0.02	0.05

[1] Adjusted for age (<35, 35–44, 45–54, 55–64, or ≥65 y), sex, study center (Detroit, Iowa, Los Angeles, or Seattle), race (white, Asian, or other), and quartiles of total energy intake.

[2] 89 observations were deleted from the analyses because of missing values. Multivariable models were also adjusted for smoking (in pack-years; nonsmoker, <7, 7–16, 17–34, or ≥35), family history of NHL, BMI (in kg/m^2; <20, 20–24.9, 25–29.9, or ≥30), exercise (in weekly metabolic equivalents; no exercise, 30–270, 271–675, 676–1080, or >1080), education (in y; <12, 12–15, or ≥16), quartiles of ethanol consumption (in g/wk), and quartiles of dietary fiber (in g/d).

(**Table 6**). Similar to the associations found for all NHL types, intakes of vegetables (total, green leafy, and cruciferous) and lutein and zeaxanthin were inversely associated with the 2 subtypes (data not shown). However, the test for OR heterogeneity was significant between the 2 NHL subtypes for the variables listed in Table 6; all variables except dietary lycopene showed stronger inverse associations with diffuse than with follicular NHL subtype.

Finally, we observed no significant differences in the effect estimates of most foods and nutrients with NHL between the nutrient residual and standard multivariable methods of energy-adjustment. However, the associations between NHL and the highest quartile of dietary vitamin E intake were stronger with the standard multivariable method (OR: 0.51; 95% CI: 0.27, 0.94; *P* for trend = 0.09) than with the nutrient residual method (Table 4). The associations between NHL and dietary zinc (OR: 0.65; 95% CI: 0.32, 1.32; *P* trend = 0.30) and total zinc (OR: 0.79; 95% CI: 0.48, 1.29; *P* trend = 0.53) intakes were not statistically significant with the standard multivariable method, but strengthened and became significant with the nutrient residual method (Table 4).

DISCUSSION

We found inverse associations between NHL risk and higher intakes of all vegetables combined, but particularly with green leafy and cruciferous vegetables, and with higher intakes of the

TABLE 4
Odds ratios (ORs) and 95% CIs of the association between daily intakes of antioxidants and related nutrients and non-Hodgkin lymphoma in the National Cancer Institute–Surveillance, Epidemiology, and End Results Study (1998–2000)[1]

Nutrient	Control subjects	Case subjects	OR (95% CI)[2]	Multivariate model OR (95% CI)[3]
	n	*n*		
Dietary vitamin A (RE/d)				
≤761	98	147	1.00	1.00
762–980	98	116	0.90 (0.62, 1.32)	1.04 (0.67, 1.60)
981–1213	98	97	0.77 (0.51, 1.15)	0.77 (0.48, 1.21)
>1213	97	106	0.94 (0.63, 1.40)	1.04 (0.64, 1.67)
P for trend			0.59	0.81
Total vitamin A (RE/d)[4]				
≤5736	98	140	1.00	1.00
5737–8657	98	123	0.90 (0.61, 1.33)	0.80 (0.52, 1.23)
8658–11682	98	103	0.83 (0.56, 1.23)	0.71 (0.46, 1.11)
>11682	97	100	0.90 (0.60, 1.35)	0.75 (0.47, 1.20)
P for trend			0.52	0.19
Dietary α-carotene (μg/d)				
≤155	98	153	1.00	1.00
156–246	98	110	0.77 (0.52, 1.13)	0.76 (0.49, 1.19)
247–398	98	105	0.76 (0.51, 1.12)	0.69 (0.44, 1.11)
>398	97	98	0.75 (0.50, 1.11)	0.75 (0.45, 1.24)
P for trend			0.14	0.23
Dietary β-carotene (μg/d)				
≤1666	98	162	1.00	1.00
1667–2433	98	102	0.65 (0.44, 0.96)	0.63 (0.40, 0.97)
2434–3637	98	107	0.69 (0.47, 1.02)	0.72 (0.46, 1.13)
>3637	97	95	0.68 (0.46, 1.02)	0.75 (0.45, 1.25)
P for trend			0.08	0.31
Total β-carotene (μg/d)[4]				
≤2148	98	149	1.00	1.00
2149–3427	98	134	0.97 (0.66, 1.42)	1.02 (0.66, 1.56)
3428–5105	98	75	0.53 (0.35, 0.80)	0.55 (0.34, 0.89)
>5105	97	108	0.84 (0.57, 1.26)	0.87 (0.54, 1.42)
P for trend			0.10	0.23
Dietary β-cryptoxanthin (μg/d)				
≤53	98	119	1.00	1.00
54–128	98	127	1.10 (0.75, 1.61)	1.12 (0.72, 1.74)
129–227	98	124	1.12 (0.76, 1.65)	1.29 (0.82, 2.03)
>227	97	96	0.95 (0.63, 1.43)	1.10 (0.68, 1.78)
P for trend			0.88	0.58
Dietary lutein and zeaxanthin (μg/d)				
≤1215	98	167	1.00	1.00
1216–1914	98	107	0.61 (0.41, 0.90)	0.63 (0.41, 0.99)
1915–3034	98	113	0.66 (0.45, 0.98)	0.79 (0.50, 1.24)
>3034	97	79	0.49 (0.32, 0.74)	0.54 (0.32, 0.91)
P for trend			0.002	0.06
Dietary lycopene (μg/d)				
≤2995	98	117	1.00	1.00
2996–4364	98	129	1.02 (0.69, 1.50)	1.01 (0.65, 1.56)
4365–5891	98	88	0.68 (0.45, 1.02)	0.73 (0.46, 1.16)
>5891	97	132	1.02 (0.69, 1.51)	1.15 (0.72, 1.84)
P for trend			0.64	0.82
Dietary vitamin E (α-TE/d)				
≤6.9	98	123	1.00	1.00
7.0–8.1	98	121	1.00 (0.68, 1.48)	1.12 (0.73, 1.74)
8.2–9.6	98	119	0.93 (0.63, 1.38)	0.93 (0.60, 1.44)
>9.6	97	103	0.77 (0.51, 1.14)	0.81 (0.52, 1.27)
P for trend			0.18	0.26
Total vitamin E (α-TE/d)[4]				
≤11	98	131	1.00	1.00
12–29	98	114	0.71 (0.48, 1.06)	0.70 (0.45, 1.09)
30–276	98	113	0.88 (0.60, 1.31)	0.87 (0.57, 1.35)
>276	97	108	0.87 (0.58, 1.30)	0.89 (0.57, 1.40)
P for trend			0.72	0.85

(*Continued*)

TABLE 4 (*Continued*)

Nutrient	Control subjects	Case subjects	OR (95% CI)[2]	Multivariate model OR (95% CI)[3]
	n	*n*		
Dietary vitamin C (mg/d)				
≤61	98	134	1.00	1.00
62–92	98	130	0.99 (0.68, 1.45)	1.03 (0.64, 1.54)
93–123	98	116	0.95 (0.64, 1.39)	1.12 (0.69, 1.70)
>123	97	86	0.71 (0.48, 1.07)	0.80 (0.50, 1.26)
P trend			0.12	0.47
Total vitamin C (mg/d)[4]				
≤100	98	145	1.00	1.00
101–168	98	116	0.96 (0.65, 1.42)	1.14 (0.73, 1.77)
169–476	98	107	0.77 (0.52, 1.15)	0.84 (0.53, 1.33)
>476	97	98	0.83 (0.55, 1.24)	0.86 (0.55, 1.37)
P for trend			0.22	0.30
Dietary zinc (mg/d)				
≤7.8	98	147	1.00	1.00
7.9–9.8	98	122	0.84 (0.57, 1.23)	0.86 (0.56, 1.32)
9.9–12.8	98	116	0.76 (0.51, 1.11)	0.74 (0.48, 1.15)
>12.8	97	81	0.59 (0.39, 0.88)	0.58 (0.36, 0.91)
P for trend			0.01	0.02
Total zinc (mg/d)[4]				
≤10	98	128	1.00	1.00
11–15	98	126	0.73 (0.49, 1.10)	0.76 (0.48, 1.19)
16–26	98	135	0.94 (0.63, 1.39)	1.00 (0.65, 1.56)
>26	97	77	0.68 (0.45, 1.02)	0.58 (0.36, 0.91)
P for trend			0.17	0.08

[1] RE, retinol equivalents; α-TE, α-tocopherol equivalents.

[2] Adjusted for age (<35, 35–44, 45–54, 55–64, or ≥65 y), sex, study center (Detroit, Iowa, Los Angeles, or Seattle), race (white, Asian, or other), and quartiles of total energy intake.

[3] 89 Observations were deleted from the analyses because of missing values. Multivariable models were also adjusted for smoking (in pack-years; nonsmoker, <7, 7–16, 17–34, or ≥35), family history of non-Hodgkin lymphoma, BMI (in kg/m^2; <20, 20–24.9, 25–29.9, or ≥30), exercise (in weekly metabolic equivalents; no exercise, 30–270, 271–675, 676–1080, or >1080), education (in y; <12, 12–15, or ≥16), quartiles of ethanol consumption (in g/wk), and quartiles of dietary fiber (in g/d).

[4] Combination of dietary and supplemental intakes.

nutrients lutein and zeaxanthin and zinc. Some of these associations appeared more pronounced in active participants and in those with a diffuse NHL subtype. Importantly, the choice of energy-adjustment method could give spurious results and requires careful consideration in analyses of dietary intake.

TABLE 5
Multivariable-adjusted odds ratios (ORs) and 95% CIs of the association between antioxidant-related foods and nutrients and non-Hodgkin lymphoma subtype, stratified by exercise level, in the National Cancer Institute–Surveillance, Epidemiology, and End Results Study (1998–2000)[1]

Exercise	Green leafy vegetables	Lutein and zeaxanthin
<510 METS/wk	1.19 (0.60, 2.35)	1.27 (0.60, 2.65)
P for trend	0.80	0.54
≥510 METS/wk	0.33 (0.16, 0.70)	0.27 (0.12, 0.61)
P for trend	0.002	0.003
P for interaction	0.004	0.01

[1] ORs were obtained by comparing the highest with the lowest quartile of intake. METS, metabolic equivalents. Adjusted for age (<35, 35–44, 45–54, 55–64, or ≥65 y), sex, study center (Detroit, Iowa, Los Angeles, or Seattle), race (white, Asian, or other), quartiles of total energy intake, smoking (in pack-years; nonsmoker, <7, 7–16, 17–34, or ≥35), family history of non-Hodgkin lymphoma, BMI (in kg/m^2; <20, 20–24.9, 25–29.9, or ≥30), education (in y; <12, 12–15, or ≥16), quartiles of ethanol consumption (in g/wk), and quartiles of dietary fiber (in g/d).

Other studies have reported similar inverse associations between NHL incidence and higher intake of all (3), cruciferous (3–5), and dark green (4, 6) vegetables. Collectively, these vegetables contain lutein and zeaxanthin (32)—nutrients also inversely associated with NHL in our study—the vitamin folate, which is involved in pathways of DNA synthesis, repair, and methylation reactions (33, 34), and glucoinolates, which are converted in vivo to isothiocyanates, compounds that are potent inducers of carcinogen-detoxifying enzymes (35). In a companion article, we found that the association of higher dietary folate was inversely related to NHL (OR: 0.73; 95% CI: 0.44, 1.21) and reached statistical significance with diffuse-type NHL (36). Studies showed inverse associations between cruciferous vegetables and several cancers, particularly in carriers of the null genotype of the family of phase II conjugating (detoxification) enzymes, ie, glutathione *S*-transferases (37–42). Induction of phase II detoxification enzymes reduces exposure of the target tissue to DNA damage and may block the initiation stage of chemical carcinogenesis (35). We also observed a reduced risk of NHL with increasing servings of tomato products, although this was not statistically significant after multivariable adjustment. One other study reported a significant 70% risk reduction with >1 serving tomato products/wk (5). The risk reduction may be attributable to lycopene, which was not assessed in that study and showed no association with NHL in our study, or to other nutrients found in tomatoes such as folate and vitamins C and E (43),

TABLE 6
Multivariable-adjusted odds ratios (ORs) and 95% CIs of the association between antioxidant-related foods and nutrients and non-Hodgkin lymphoma (NHL) subtypes in the National Cancer Institute–Surveillance, Epidemiology, and End Results Study (1998–2000)[1]

Food group	Follicular NHL (n = 118)	Diffuse NHL (n = 167)	P for heterogeneity
Fruit including juices (servings/wk)			
≤8	1.00	1.00	
8.5–15	1.24 (0.61, 2.55)	1.00 (0.55, 1.80)	
15.5–23	1.96 (0.94, 4.10)	0.97 (0.51, 1.85)	
>23	1.31 (0.57, 3.01)	0.63 (0.30, 1.30)	0.01
P for trend	0.34	0.35	
Citrus fruit including juices (servings/wk)			
≤1	1.00	1.00	
1.5–3.5	1.92 (0.94, 3.93)	1.26 (0.72, 2.18)	
4–6.5	1.85 (0.86, 3.97)	0.71 (0.38, 1.33)	
>6.5	2.83 (1.33, 6.00)	0.81 (0.42, 1.54)	0.001
P for trend	0.06	0.27	
Dietary β-cryptoxanthin (μg/d)			
≤53	1.00	1.00	
54–128	1.65 (0.77, 3.53)	0.84 (0.47, 1.51)	
129–227	2.89 (1.35, 6.17)	0.99 (0.54, 1.82)	
>227	2.96 (1.35, 6.50)	0.58 (0.29, 1.15)	0.0004
P for trend	0.01	0.22	
Dietary lycopene (μg/d)			
≤2995	1.00	1.00	
2996–4364	0.88 (0.45, 1.71)	1.19 (0.65, 2.21)	
4365–5891	0.70 (0.34, 1.45)	0.96 (0.50, 1.83)	
>5891	0.68 (0.32, 1.42)	1.63 (0.86, 3.08)	0.02
P for trend	0.22	0.35	
Dietary vitamin C (mg/d)			
≤61	1.00	1.00	
62–92	1.00 (0.49, 2.03)	0.97 (0.53, 1.76)	
93–123	1.51 (0.75, 3.06)	1.14 (0.62, 2.11)	
>123	1.28 (0.59, 2.80)	0.51 (0.25, 1.06)	0.01
P for trend	0.48	0.17	
Total vitamin C (mg/d)[2]			
≤100	1.00	1.00	
101–168	2.04 (1.02, 4.08)	0.86 (0.48, 1.54)	
169–476	1.37 (0.65, 2.86)	0.60 (0.32, 1.11)	
>476	1.38 (0.66, 2.88)	0.58 (0.31, 1.10)	0.01
P for trend	0.90	0.04	
Total zinc (mg/d)[2]			
≤10	1.00	1.00	
11–15	0.67 (0.33, 1.37)	0.81 (0.45, 1.48)	
16–26	1.21 (0.61, 2.40)	1.00 (0.55, 1.80)	
>26	0.77 (0.38, 1.56)	0.30 (0.14, 0.62)	0.01
P for trend	0.67	0.01	

[1] ORs were adjusted for age (<35, 35–44, 45–54, 55–64, or ≥65 y), sex, study center (Detroit, Iowa, Los Angeles, or Seattle), race (white, Asian, or other), quartiles of total energy intake, smoking (in pack-years; nonsmoker, <7, 7–16, 17–34, or ≥35), family history of non-Hodgkin lymphoma, BMI (in kg/m^2; <20, 20–24.9, 25–29.9, or ≥30), education (in y; <12, 12–15, or ≥16), quartiles of ethanol consumption (in g/wk), and quartiles of dietary fiber (in g/d).
[2] Combination of dietary and supplemental intakes.

which alone showed inverse, though nonsignificant, associations with NHL in our study but when considered together may contribute importantly to risk. In addition to the ROS-scavenging role of carotenoids and antioxidant-related nutrients (44), it has been suggested that they can also enhance DNA repair activity by modifying gene expression distinct from their direct antioxidant properties (45). Our findings agree with most previous investigations that found no significant association between NHL and intakes of fruit (3, 5, 8, 9, 11, 12) and intakes of individual vitamins A, C, and E and specific carotenoids, regardless of whether they were dietary or supplemental intakes (3, 5, 7, 13, 46).

A potentially important observation in this analysis was the inverse association between zinc and NHL; that the association was consistent with both dietary and supplemental sources argues against multivitamin use as the exposure of interest. Zinc can physically displace DNA-bound iron, thereby reducing the extent of iron-catalyzed hydroxyl radical production, such that as intracellular concentrations of zinc rise, more iron may be displaced from nucleoproteins and less hydroxyl radical–driven DNA damage may occur (47). Zinc also has widespread action on different enzymes, peptides, transcriptional factors, and cytokines that are involved in various physiologic steps of immune

development and reactivity (48, 49). Zinc is a component of several single-strand DNA binding proteins including replication protein A, DNA glycosylase, and endonuclease IV, which are essential for DNA replication and mismatch repair (47). Evidence suggests that the activity of zinc-containing DNA binding domains of proteins progressively diminishes as the environment becomes increasingly prooxidant (47) and this may interfere with genomic stability. Preliminary findings of supplementation with 45 mg elemental Zn/d in 5 healthy volunteers compared with placebo-treated volunteers showed a reduction by almost 50% of nuclear transcription factor κB binding to DNA, a marker of ROS production (50). Given the ubiquitous involvement of zinc in numerous metabolic processes, chronic marginal intakes may lead to inadequate host defense mechanisms and predispose to insults such as DNA breaks and early neoplastic transformations.

Our suggestive finding of inverse associations between NHL and higher intakes of green leafy vegetables and lutein and zeaxanthin in participants with higher physical activity may indicate neutralization of exercise-induced ROS production by these vegetables and nutrients (51). Exercise results in increased amounts of malondialdehyde in blood, an indirect indicator of lipid peroxidation. Subjects given supplemental intakes of different antioxidants showed reduced malondialdehyde concentrations after exercising compared with those who were given placebo, which suggests that antioxidants may offer some protection against exercise-induced ROS production (51).

Other studies that examined associations by NHL subtype (3, 5, 9) generally reported similar findings across subtypes, although diffuse NHL was inversely related to α-carotene (5) and yellow and orange vegetables (9) and positively associated with retinol (5). Follicular NHL was inversely related to intakes of total vegetables (9, 4) and fruit (4), particularly in women (4). We found similar associations of foods and nutrients across NHL subtypes, although higher intakes of all fruit and citrus fruit, dietary β-cryptoxanthin, dietary and total vitamin C, and total zinc were more strongly related to diffuse than to follicular NHL subtype; however, our findings were based on a small number of cases and require replication.

Our study has several strengths. It is one of the largest studies of diet and NHL risk conducted across multiple centers that stratified NHL by common subtype. To our knowledge, our study is the first epidemiologic report of the associations between zinc and NHL. We used a validated food-frequency questionnaire to assess diet, with adjustment for several potentially important confounding variables including total energy and dietary fat intakes, and incorporated the most recently updated values for carotenoid content of fruit and vegetables. Ascertainment with Surveillance, Epidemiology, and End Results tumor registries ensured that few cases were missed, and the use of population controls minimized some of the biases associated with hospital-based case-control studies. Furthermore, our analyses compared 2 methods of adjustment for total energy, given the reported differences in effect estimates across methods when the categorical form of the dietary variable is used (52, 53). Some differences were noted across methods for those variables that appeared to have higher correlations with total energy intake. In instances where the true associations between diet and disease are unknown, correlated errors may lead to distortion of the underlying associations (30). Our findings suggest that the nutrient residual method may circumvent these problems, as reported elsewhere (30).

Our study also has potential limitations. First, our response was low. However, we found similar distributions in demographic characteristics between the cases and controls in the present analyses compared with all eligible cases and controls, which provided reassurance that the overall low control response did not bias our effect estimates appreciably. Second, as with any case-control design, recall bias is a concern; reassuringly, our findings agree with those from a large cohort study in which diet was assessed prospectively (3). Third, supplemental data were not available for all vitamins and minerals, which may underestimate true associations between some antioxidants and NHL. Finally, some degree of error in the measurement of diet and lifestyle variables is to be expected, and random misclassification of exposure between cases and controls would have attenuated the associations.

These data, in combination with other case-control and cohort studies, suggest that higher intakes of vegetables, in general, and specific nutrients that function in antioxidant-related pathways, in particular, may reduce the risk of developing NHL. If so, dietary change may be one of a small number of modifiable influences on lymphoma risk. Our observation of a stronger link in active persons and in those with diffuse NHL subtypes requires corroboration in other studies. The effect of foods and nutrients may be further clarified within the context of polymorphisms of genes that participate in the repair of oxidative damage.

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JRC, SD, MS, WC, JC, PH, and MHW were involved in the study design. LEK and JRC directed the data analysis. LEK and MHW guided the process for incorporating updated carotenoid values in the analyses. LEK wrote the initial draft of the manuscript. UL was involved in the editing and writing of the manuscript and provided intellectual content. All authors contributed to the final manuscript. None of the authors declared any personal or financial conflict of interest.

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